


## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100945-1 WO	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/SE 03/02004	International filing date (day/month/year) 18.12.2003	Priority date (day/month/year) 20.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D211/26		
Applicant ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:
- I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand  25.06.2004	Date of completion of this report  30.05.2005
Name and mailing address of the International preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Schuemacher, A Telephone No. +49 89 2399-7818



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**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-27 as originally filed

**Claims, Numbers**

1-11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

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**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 8,10,11

because:

☒ the said international application, or the said claims Nos. 8,10,11 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	1-11
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-7,9
	No: Claims	

2. Citations and explanations

**see separate sheet**

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 8, 10 and 11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Novelty, Article 33(2) PCT:**

Reference is made to the following document:

D1: STEVENSON ET AL.: '4,4-Disubstituted Piperidine High-Affinity NK1 Antagonists: Structure-Activity Relationships and in Vivo Activity' J. MED. CHEM. vol. 41, 1998, pages 4623 - 4635, XP002173109

With regard to the prior art disclosed in D1, the subject-matter of the present application, i.e. the compounds of formula (I) according to current claim 1, appears to fulfil the requirements of novelty, cf. Article 33(2) PCT. In fact, the claimed compounds differ from those disclosed in D1 because of the naphthalene ring ever present in the claimed compounds.

**2. Inventive step, Article 33(3) PCT:**

The present application is related to 4-phenyl-4-[(naphth-1-yl)methylaminomethyl] piperidine compounds of formula (I) according to present claim 1, having dual NK1 antagonist activity and SSRI activity and thus, useful to treat central nervous system (CNS) disorders (see p.2, I.15-18).

Di discloses also 4-phenyl-4-arylmethoxymethyl-piperidines as high affinity NK1 antagonists. Compounds, wherein the methoxymethyl chain was replaced by a methylaminomethyl chain were prepared and tested in D1 (compounds 48 and 49): it is however stated on p.4628 that these compounds have poor affinity for the NK1 receptor.

Thus, the skilled person, looking for further NK1 antagonists would not be led to replace the

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methoxymethyl chain by a methylaminomethyl.

Additionally there is no indication in this document that would suggest to the skilled person, looking for further NK1 antagonists, to replace the terminal phenyl by a naphthalene ring.

Due to the structural differences re the active compounds in D1 (the replacement of the methoxymethyl by a methylaminomethyl and the replacement of the phenyl by a naphthalene ring), it cannot be said with any degree of accuracy that the skilled person, faced with the problem of providing further novel compounds with NK1 antagonistic activity, would have been unambiguously led to prepare the compounds of the present application.

For the purpose of assessing the inventive step during the International Preliminary Examination it is assumed that the claimed compounds do indeed possess the alleged dual NK1 antagonistic and SSRI activities. Thus and in absence of any more pertinent prior art, the present invention appears to involve an inventive step, based on the dual NK1 antagonistic and SSRI activities of the claimed compounds.

**3. industrial applicability:**

For the assessment of the present claims 8, 10 and 11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.